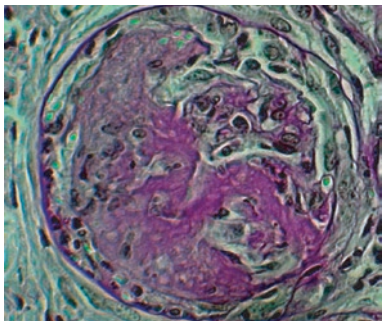
Kidney International (2010) **77,** 79. doi:10.1038/ki.2009.476

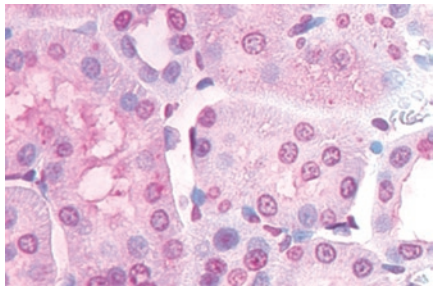
PI3K in ANCA



Anti-neutrophil cytoplasmic autoantibodies (ANCA) are associated with necrotizing crescentic glomerulonephritis and systemic vasculitis, in large part because of invading neutrophils. To investigate the signaling pathway used by neutrophils, Schreiber *et al.* transplanted bone marrow from mice that were deficient in phosphoinositol 3 kinase-γ (PI3Kγ) and then induced crescentic glomerulonephritis by injection of myeloperoxidase into myeloperoxidase-deficient mice. When wild-type bone marrow was infused into these mice, they developed the disease. However, bone marrow derived from mice that were deficient in PI3Kγ were protected from the glomerulonephritis. Similarly, treatment of the mice infused with wild-type bone marrow with an inhibitor of PI3Kγ prevented the development of the nephritis as well. These studies identify an important target for development of new therapies. Given that this molecule is under intense investigation by a number of pharmaceutical companies, the results of this preclinical study should inject some hope into the future of therapeutics for this very serious renal disease. **See page 118.**

Hydrogen water

Oxidative damage is one of the major pathogenic mechanisms in a number of diseases, especially fibrotic and inflammatory ones. Chronic allograft nephropathy is one such disease. As they report in this issue, Cardinal *et al.* have tried a new therapeutic strategy to combat oxidative damage in which they use molecular hydrogen, a reagent that can scavenge reactive oxygen species. Using a transplantation model from one rat strain to another (with bilateral nephrectomy), they fed the animals water that had been bubbled with hydrogen gas. When rats were fed unhydrogenated water for 150 days, they developed proteinuria, and the graft eventually failed. But those rats ingesting hydrogen water had improved survival, fewer inflammatory mediators, and less activation of inflammatory pathways. If these results can be transplanted to humans, they might provide an effective and cheap therapy. **See page 101.**



Calcineurin and renin secretion

Renin secretion from the juxtaglomerular apparatus (JGA) is regulated by calcium in a manner that is opposite of the classic hormone secretion paradigm. Increases in cell calcium inhibit renin release. As they report in this issue, Madsen *et al.* studied the details of the mechanism using whole-cell patch clamp studies in which they measured the capacitance of the membrane as an index of exocytosis, since an increase in capacitance is due largely to increases in membrane area. They found that inhibition of calcineurin by cyclosporin stimulated renin secretion. Calcineurin is a calcium-dependent phosphatase whose activity is dependent on calcium/calmodulin levels in the cell. Similarly, intracellular delivery of a calcineurin inhibitor peptide produced the same effect as cyclosporin. There are three genes for calcineurin A, and the JGA cells expressed only two of them: the β and γ isoforms but not the α isoform. Using mice with the β or α isoform deleted, the authors found that cyclosporin increased renin in mice with the γ isoform deleted, suggesting that the α isoform is the culprit for the effect of cyclosporin. **See page 110.**